Septic shock: A multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality

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背景

- Septic　shockの死亡率は徐々に減少しているが疾患自体は増加している
- 概算で..

2010年；934,000件

2020年；1,110,000件

- Sepsisにかかる費用も算出されている

→sepsis1件　＄22,100

一年で…＄167億!!!

背景

- SSCGでは，septic　shock出現の初期における輸液療法をearly goal directed therapy（EGDT）として重視
- resuscitation bundle とmanagement bundle

■Resuscitation bundle
①血清乳酸値測定
②抗菌薬投与前の血液培養検体2セットの採取
③抗菌薬の1時間以内の投与
④低血圧あるいは血清乳酸値＞4 mmol/Lの場合のEGDT（CVP, ScVO2, Hct, Inotropeなど）

→これらを6時間以内に達成

■Management bundle
①ショック持続における少量ステロイド療法
②活性化プロテインCの投与基準
③血糖値＜150 mg/dL
④人工呼吸管理における最大吸気圧＜30 cmH2O

→入院後の24時間以内

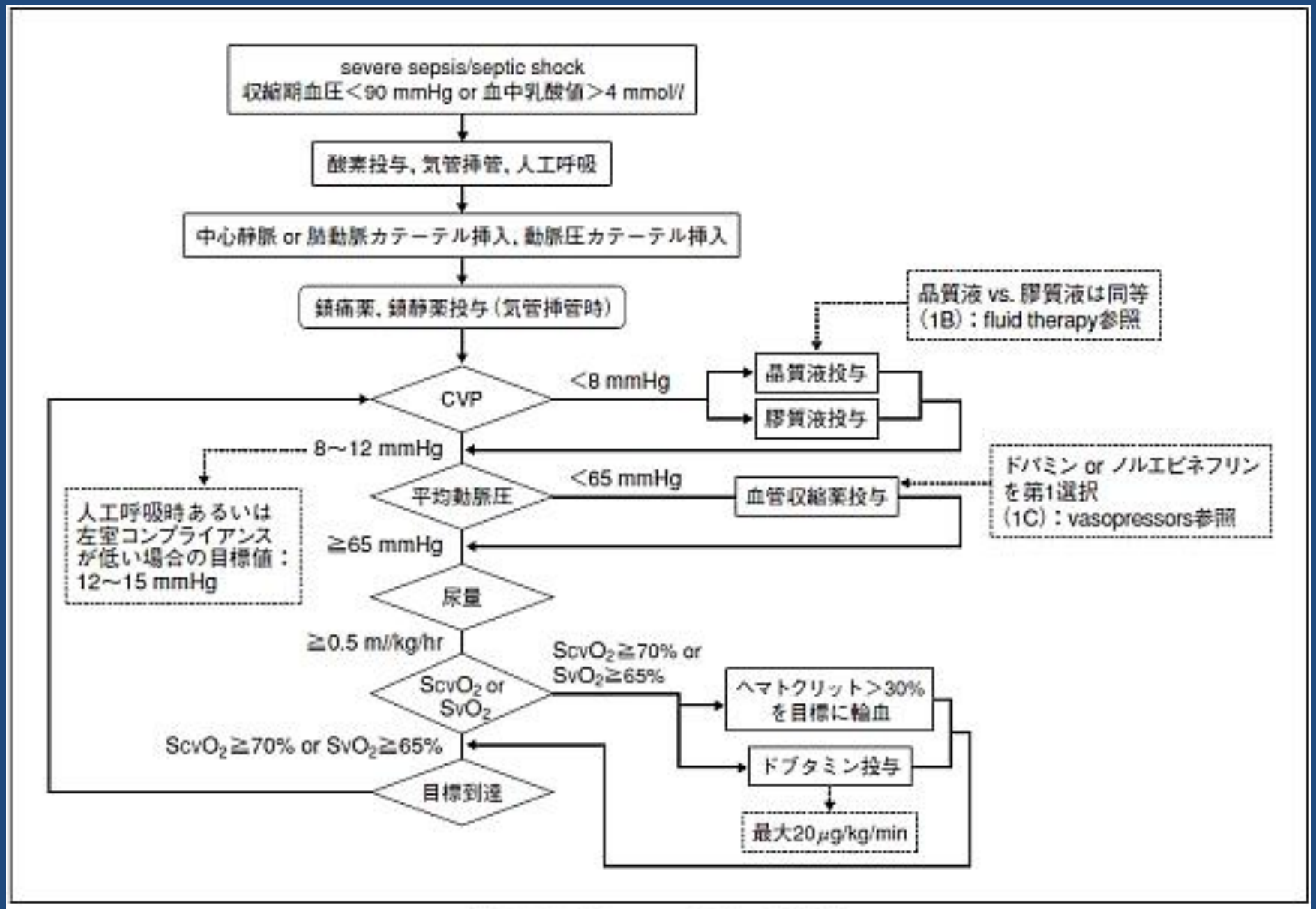

図 2　Initial resuscitationの手順

背景

- EGDTの問題点
- （generalizability/single Ctr.　CVP/ScvO2）
- 依然として高い死亡率（30-40%）
- SSCG　complianceは低い
  （ｽﾍﾟｲﾝ5.3-10%　2008JAMAのｽﾀﾃﾞｨは有名）
- “code　sepsis”@ﾍﾞｽｲｽﾗｴﾙ
  →RRSでｺﾝﾌﾟﾗｲｱﾝｽ上昇..しかし臨床的outcomeは不明
- こうした介入がとりわけresuscitation　bundleのｺﾝﾌﾟﾗｲｱﾝｽや患者予後を変えるかどうか

Material&Method

- severe sepsis/septic shock admitted to MICU@Mayo Clinic
- January 2007 →September 2009
- 候補者は感染疑う下記の条件
  - aged 18 yrs
  - systolic blood pressure 90 mm Hg
  - despite fluid challenge with 20 mL/kg of crystalloid
  - lactate level 4mmol/L

Material&Method

- 除外基準
  - refused resuscitation (CV留置含む)
  - active bleeding
  - cardiogenic pulmonary edema

- Sepsis, severe sepsis, and septic shock

→定義はACCP&SCCMのもの

Material&Method

- 評価する時期
- *1) Baseline.(2001.1.1-2007.12.28)*

  →通常の教育/ｶﾝﾌｧ/M&M/ﾊﾝﾄﾞｱｳﾄ/ｵｰﾀﾞｰｾｯﾄ
- *2) Daily Auditing and Weekly Feedback.*

  （2007.12.29-2008.9.26）

  →日々の監査と週に一回の医師へのfeedback
- *3) SRT Activation :sepsis resuscitation team*

  (2008.9.27-2009.9.30)

  →24/7で対応しているﾁｰﾑが来棟　2) も継続

Table 1. The sepsis response team members and their roles

チームの構成員

Multidisciplinary Member	Role
ICU attending physician	• Identifies patients who meet criteria for sepsis protocol • 24/7 bedside supervision of the ICU team in implementing the sepsis protocol
ICU fellow	• Identifies patients who meet criteria for sepsis protocol • Acts as team leader, allocating tasks to individual team members • Supervises ICU residents during the resuscitation, including placement of central venous catheter and implementation of the sepsis protocol
ICU resident	• Identifies patients who meet criteria for sepsis protocol • Responsible for the primary management of the patient in the ICU, including placement of central venous catheter and the implementation of the sepsis protocol
ICU nurse	• Identifies patients who meet criteria for sepsis protocol • Implements the sepsis protocol following the computerized physician standing orders, including fluid boluses triggered by central venous pressure measurement
ICU pharmacist	• Identifies patients who meet criteria for sepsis protocol • Responsible for timely order processing and administration of antibiotics, vasopressors, and inotropes
Respiratory therapist	• Assists in central venous catheter placement and calibration • Arterial line placement and calibration • Assists in the management of mechanical ventilation
Vascular access technician	• Timely bedside blood lactate measurements and drawing blood samples as ordered
Unit secretary	• Aids in activation of sepsis response team paging system • Notifies portable radiology technician if needed
Portable radiology technician	• Immediate chest radiograph performed when needed

ICU, intensive care unit.

評価

- 1°　outcome
  resuscitation　bundleの項目のｺﾝﾌﾟﾗｲｱﾝｽ

- 2°　outcome
  院内死亡率

Table 2. Elements of the sepsis resuscitation bundle **7 elements**

Element	Definition
Lactate	Measured before or within 1 hr after blood culture
Blood culture	Drawn before antibiotics administered
Antibiotic	Administered within 1 hr of sepsis recognition and intensive care unit admission
Fluid resuscitation	In the event of hypotension and/or lactate >4 mmol/L, an initial bolus of 20 mL/kg (crystalloid or equivalent colloid) administered followed by subsequent fluid challenges until one of the following: • Central venous pressure ≥8 mm Hg (≥12 mm Hg if mechanical ventilation) • Mean arterial pressure ≥65 mm Hg without vasopressors and lactate <2.5 mmol/L and urine output >0.5 ml/kg/hr
Appropriate vasopressor use	Vasopressor administered for one of the following two: • Persistent MAP <65 mm Hg despite fluid challenge 20 mL/kg of crystalloid • Life-threatening hypotension with MAP <50 mm Hg for ≥15 mins Vasopressor not administered when one of the two not met
Red blood cell administration	Transfused if hematocrit <30% and $ScvO_2$ <70% or mixed venous O_2 <65% despite fluid resuscitation
Inotrope utilization	Started if Hct ≥30% and $ScvO_2$ <70% or mixed venous oxygen saturation <65% despite fluid resuscitation

MAP, mean arterial pressure.

6 hrs!!

RESULTS

- 観察期間は2007.1-2009.9　33ヶ月間
- N=984(1°　outcome)　N=962(2°　outcome)

- 患者背景→TABLE3
- Severe　sepsisは52例（5.3%）
- Septic　shockは932（94.7%）

Table 3. Baseline characteristics of 962 patients with severe sepsis or septic shock

Characteristics	Baseline (n = 267)	Weekly Feedback (n = 272)	SRT Activation (n = 423)	p
White race (%)	243 (91.0%)	243 (89.3%)	378 (89.4%)	.748
Female gender	131 (49.1)	122 (44.9)	174 (41.1)	.122
Age, mean (SD)	66.3 (16.1)	68.7 (15.6)	65.8 (15.9)	.059
Acute Physiology and Chronic Health Evaluation comorbidities (SD)	83.4	79.2	73.5	.009
Leukemia or multiple myeloma	28 (10.5)	34 (12.5)	51 (12.1)	
Metastatic tumor	18 (6.7%)	16 (5.9%)	19 (4.5%)	
Hepatic failure	16 (6.0%)	5 (1.8%)	19 (4.5%)	
Hepatic cirrhosis	12 (4.5%)	1 (0.4%)	15 (3.5%)	
Lymphoma	7 (2.6%)	1 (0.4%)	5 (1.2%)	
Immunosuppression	2 (0.7%)	0	1 (0.2%)	
None	184 (68.9%)	215 (79.0%)	313 (74.0%)	
Admission source (%)				.233
Same hospital emergency department	132 (49.4%)	118 (43.4%)	201 (47.5%)	
Hospital ward	79 (29.6%)	80 (29.4%)	272 (28.3%)	
Other hospital emergency department	31 (11.6%)	49 (18.0%)	78 (18.4%)	
Other hospital	25 (9.4%)	25 (9.2%)	31 (7.3%)	
Do not resuscitate in case of cardiac arrest (%)	30 (11.2%)	58 (21.3%)	70 (16.5%)	.007
Lactate, mean (SD), mmol/L	2.72 (2.5)	2.66 (2.03)	2.92 (2.44)	.305
Median (interquartile range), mmol/L	2.00 (1.00–3.30)	2.00 (1.10–3.65)	2.3 (1.25–3.80)	.149

resuscitation bundleのｺﾝﾌﾟﾗｲｱﾝｽに関する研究の対象者 内訳

7つのelement　それぞれのコンプライアンス

Table 4. Compliance with sepsis resuscitation bundle in 984 episodes of severe sepsis or septic shock

Bundle Element	Study Period: Baseline (n = 268)	Weekly Feedback (n = 284)	Sepsis Response Team Activation (n = 432)	p
Lactate measured	202 (75.4%)	259 (91.2%)	419 (97.0%)	<.001
Blood culture before antibiotics	235 (87.7%)	264 (93.0%)	422 (97.7%)	<.001
Timely antibiotics	207 (77.2%)	238 (83.8%)	393 (91.0%)	<.001
Adequate fluid	153 (57.1%)	182 (64.1%)	329 (76.2%)	<.001
Appropriate vasopressor	264 (93.0%)	252 (94.0%)	385 (89.1%)	.046
Appropriate red blood cell transfusion	221 (82.5%)	245 (86.3%)	370 (85.6%)	.397
Appropriate inotrope use	96 (35.8%)	158 (55.6%)	266 (61.6%)	<.001
All 7 elements	34 (12.7%)	107 (37.7%)	232 (53.7%)	<.001
Mortality　Overall；26．2%	81 (30.3%)	78 (28.7%)	93 (22.0%)	.029
平均輸液量（6時間で）	4.2L	4.8L	4.7L	有意差無し
平均ICU滞在期間	4日	4日		有意差無し

生存VS.死亡で見た場合のrisk

Table 5. Differences between survivors and nonsurvivors among 962 patients with severe sepsis or septic shock

Characteristic	Nonsurvivors (n = 252)	Survivors (n = 710)	p
White race	230 (91.3%)	634 (89.3%)	.373
Female gender	125 (49.6%)	302 (42.5%)	.052
Age, mean (SD), years	68.6 (16.1)	66.1 (15.8)	.539
Acute Physiology and Chronic Health Evaluation comorbidities			<.001
Leukemia or multiple myeloma	38 (15.1%)	75 (10.6%)	
Metastatic tumor	13 (5.2%)	40 (5.6%)	
Hepatic failure	19 (7.5%)	21 (3.0%)	
Hepatic cirrhosis	13 (5.2%)	15 (2.1%)	
Lymphoma	4 (1.6%)	9 (1.3%)	
Immunosuppression	2 (0.8%)	1 (0.1%)	
None	163 (64.7%)	549 (77.3%)	
Admission source			<.001
Same hospital emergency department	100 (39.7%)	351 (49.4%)	
Hospital ward	97 (38.5%)	175 (24.6%)	
Other hospital emergency department	34 (13.5%)	124 (17.5%)	
Other hospital	21 (8.3%)	60 (8.5%)	
Do not resuscitate in case of cardiac arrest	51 (20.2%)	107 (15.1%)	.057
Lactate, mean (SD), mmol/L	3.16 (2.83)	2.74 (2.17)	<.001

2° outcome；それぞれの因子の院内医死亡への関与

Table 6. Multiple logistic regression analysis showing the association of hospital death with the study intervention periods and other factors

Predictor Variable	Odds Ratio (95% Confidence Interval)	p
Female gender	1.329 (0.983–1.796)	.065
Acute Physiology and Chronic Health Evaluation comorbidities		
None	1	
Hepatic cirrhosis	3.313 (1.509–7.275)	.003
Hepatic failure	3.113 (1.598–6.066)	.001
Leukemia or multiple myeloma	1.677 (1.079–2.608)	.022
Lymphoma	1.486 (0.441–5.006)	.523
Immunocompromised	6.872 (0.556–84.961)	.133
Metastatic tumor	1.097 (0.564–2.134)	.784
Intensive care unit admission source		
Same hospital emergency department	1	
Same hospital ward	2.088 (1.476–2.953)	<.001
Other hospital emergency department	1.050 (0.666–1.654)	.835
Other hospital ward	1.241 (0.705–2.187)	.455
Do not resuscitate at recognition of severe sepsis or septic shock	1.492 (1.011–2.202)	.044
Lactate level	1.076 (1.012–1.144)	.019
Study period		
Baseline	1	
Weekly feedback	1.013 (0.685–1.497)	.950
Sepsis response team	0.657 (0.456–0.945)	.023

☆SRT出動で7つのelementの達成は47.5%→60.8%までupした
☆但し死亡率は20.4% vs. 23.1%と有意差無し

7elementsとmortalityの関係　　()内は施設での達成率

Table 7. The relationship between mortality and compliance with the overall and each bundle element

Bundle Element	Goal Achieved	Goal Not Achieved	p
Lactate measured (94.2%)	212 of 860 (24.7%)	40 of 102 (39.2%)	.002
Blood culture before antibiotics (84.9%)	230 of 900 (25.6%)	22 of 62 (35.5%)	.085
Timely antibiotics 3時間以内で(82.3%)	202 of 818 (24.7%)	50 of 144 (34.7%)	.012
Adequate fluid	182 of 650 (28.0%)	70 of 312 (22.4%)	.066
Appropriate vasopressor (79.7%)	236 of 880 (26.8%)	16 of 82 (19.5%)	.150
Appropriate red blood cell transfusion	207 of 818 (25.3%)	45 of 144 (31.3%)	.135
Appropriate inotrope use	119 of 505 (23.6%)	133 of 457 (29.1%)	.051
All 7 elements	80 of 359 (22.3%)	172 of 603 (28.5%)	.033

☆乳酸を測定して、抗菌薬

☆注意!!　上記施設ではCV挿入32.8%　ScvO2　12.5%　CVP目標18%　inotrope使用11.9%

DISCUSSION

- Weekly feedbackやSRTチームがsepsis初期のケアと死亡率に及ぼす影響
- これらがあることでresuscitation bundleのコンプライアンスは12.7%→53.7%（Table4）
- 院内死亡率も低下した（30.3%→22%）
- 2001NEJM Riverら

  46.3%（ctrl）→30.5%(EGDT)
- 2006SHOCK Linら

  71.3%（ctrl）→53.7%(EGDT)

過去のstudyと比較してもベースの死亡率は低い群ではある..

DISCUSSION

- 比較的元気な人に対するresuscitation bundleは不要とする意見もある

  →今回、それは有用だと示された
- Feedbackだけでは不十分でSRTが死亡率を下げる
- 死亡率を上げる因子が多くてもSRT関与で死亡率下がった

  →intensivist真骨頂

DISCUSSION

- 病棟はsepsisの信号の発見の遅れとresuscitation　bundle開始の遅れが問題

- これまでsepsisに関する教育でｺﾝﾌﾟﾗｲｱﾝｽが上昇するというｽﾀﾃﾞｨはあった
- 今回はSRTも登場、この効果を検証した

limitation

- 単施設であること
- EDからの入院が約半数であるがICUsettingで、どの程度の速度で診療されていたか不明
- RCTではない
- SRTの質が評価されていない

- 現在多施設での検討を実施中..

Conclusion

- FeedbackとSRTで死亡率まで下げた
- 抗菌薬と乳酸
- Intensivistの新たな分野
- RRSのカバーできるかも？
- 下記のEGDTの追試研究結果が待たれる
  - ANZICSの研究　NCT00975793
  - East Carolina University　NCT00510835